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Antisocial Behavior and Polymorphisms in the Oxytocin Receptor Gene: Findings in Two Independent Samples

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Study concept and design: Hovey, Westberg, Lichtenstein, Anckarsäter, Lundström. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Hovey. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Hovey, Lindstedt, Johansson. Obtained funding: Westberg, Lichtenstein, Anckarsäter, Lundström. Study supervision: Westberg. No conflicts of interest reported by any of the authors.

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At a glance

- Investigation of oxytocin receptor gene (*OXTR*) variants and antisocial behavior in two independent samples (N=2,372; N=1,232) of adolescents.
- Two independent *OXTR* SNPs, rs7632287 and rs4564970 were significantly associated ($p=1.5e^{-7}$ and $p=6.3e^{-4}$, respectively) with antisocial behavior in boys.
- The association between self-reported delinquency and rs7632287 was confirmed in the replication sample.

Abstract

Importance: The quantitative genetic contribution to antisocial behavior is well established, but few, if any, genetic variants are established as risk factors. Emerging evidence suggests that the neuropeptide oxytocin may modulate interpersonal aggression.

Objective: To investigate whether single nucleotide polymorphisms in the oxytocin receptor gene are associated with the expression of antisocial behavior.

Design, setting, and participants: A discovery sample, including both sexes, was drawn from the Child and Adolescent Twin Study of Sweden (CATSS; $n=2,372$), and a sample from the Twin Study of Child and Adolescent Development (TCHAD; $n=1,232$) was used for replication. The participants were assessed for antisocial behavior, measured as continuous traits. Eight single nucleotide polymorphisms in the oxytocin receptor gene, selected on previous associations with social and antisocial behavior, were then genotyped in the participants of CATSS. Significant polymorphisms were subsequently genotyped in TCHAD for replication.

Main outcomes and measures: Participants completed self-assessment questionnaires – Life History of Aggression (available only in CATSS), and Self-Reported Delinquency (available in both samples) – designed to capture antisocial behavior.

Results: In the discovery sample, the rs7632287 AA genotype was associated with higher frequency of antisocial behavior in boys, and this was then replicated in the second sample. In particular, overt aggression (directly targeting another individual) was strongly associated with this genotype in boys ($p=6.2 \times 10^{-7}$ in the discovery sample). Meta-analysis of the results for antisocial behavior from both samples yielded $p=2.5 \times 10^{-5}$. Furthermore, an association between rs4564970 and Life History of Aggression ($p=0.00013$) survived correction in the discovery sample, but there was no association with the Self-Reported Delinquency in the replication sample.

Conclusions and relevance: We conclude that the rs7632287 and rs4564970 polymorphisms in the oxytocin receptor gene may independently influence antisocial behavior in adolescent boys. Further replication of our results will be crucial to understanding how aberrant social behavior arises, and supports the oxytocin receptor as one potential target in the treatment of aggressive antisocial behavior.

Introduction

Antisocial behavior, defined as violations of legal or social norms, constitutes a problem for all societies. Its consequences are not only the suffering of victims of violence or other crime, but also the increased risk of perpetrators for e.g. substance abuse and psychosocial problems.¹ In addition it generates a significant financial burden on society.² The causes of antisocial behavior include environmental factors, and growing evidence indicates that multiple genetic factors may help explain the variability of developing antisocial behavior.³

Oxytocin (OXT) has garnered much attention for its proposed effects on social behavior. In rodents, OXT affects e.g. social interaction, social recognition, and pair bonding.⁴ Cerebrospinal fluid levels of OXT in human newborns have been positively correlated with degree of interest in social interaction.⁵ Exogenously administered OXT affects various social behaviors, including trust,⁶ facial recognition,^{7,8} emotion recognition,⁹ and attention to socially relevant information.¹⁰ Furthermore, there is growing interest in the effects of the OXT system on antisocial behavior as well. Several studies have shown a relationship between OXT and aggression in rodents.¹¹⁻¹⁶ An increasing number of studies have investigated the relation between OXT and antisocial behavior in humans. Higher levels of autoreactive antibodies for OXT, and low OXT levels in cerebrospinal fluid, have been associated with aggressive and delinquent behavior.^{17,18} In line with this, single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene (*OXTR*) have been reported to modulate the relationship between alcohol consumption and aggression,^{19,20} to associate with callous-unemotional traits in children,^{21,22} and to increase the risk of extreme, persistent, childhood-onset aggression.^{23,24} Furthermore, higher methylation of *OXTR* has been associated with lower OXT plasma levels and higher callous-unemotional traits in adolescents with conduct problems.^{25,26} Recent studies have found interaction effects between *OXTR* SNPs and stressful life events/social stress on delinquent behavior in adolescents and peer problems in boys.^{27,28} Taken together, these results indicate that SNPs in *OXTR* could influence the plasma levels or function of the hormone, resulting in a hypo-

oxytocinergic state, which may be hypothesized to influence antisocial behavior, in particular interpersonal aggression.

Several of the above-mentioned genetic association studies have investigated groups with extreme phenotypes, or focused on interacting effects of *OXTR* SNPs and alcohol consumption or stress. Most of these studies have also been limited in the size of their populations. However, antisocial behavior most likely exists on a spectrum which is dimensionally distributed in the general population, and the demarcation is arguably quantitative rather than qualitative. In light of this, general population samples should have a larger chance to find true associations.²⁹ Using two independent population samples recruited from the Swedish general population, we proceeded to model aggressive antisocial behavior as a continuous trait, upon which we hypothesized that variations in *OXTR* would have an influence.

Methods

Participants

The discovery sample was a subsample of the Child and Adolescent Twin Study in Sweden (CATSS), an ongoing nation-wide study targeting all twins born in Sweden since July 1992, with an overall response rate of 80% at age 9.³⁰ By the age of 18, the twins are contacted again, to collect information about e.g. aggression and antisocial behavior. The retention rate in this wave is 50%. Our sample included twins aged 18 who had completed the instruments described below and submitted DNA samples. Information was available for 2,372 individuals (1,021 boys; 1,351 girls), including 494 monozygotic (MZ) twin pairs, 684 dizygotic (DZ) twin pairs, and 16 individuals without their co-twin. Ten individuals were excluded due to documented brain damage (most commonly cerebral palsy) or a known genetic syndrome (most commonly Down syndrome). Zygosity was determined using a panel of 47 SNPs.³¹ The ethnicity was determined to be Caucasian or non-Caucasian using the self-reported place of birth of the parents. The sample consisted of 0.46% non-Caucasians (n=11), defined as subjects having one parent born in countries where the population has a majority of non-Caucasians. CATSS was approved by the Ethics Committee at Karolinska Institutet, and participants were protected by the informed consent procedure.

The replication sample was a subsample of The Swedish Twin Study of Child and Adolescent Development (TCHAD), including 1,480 twin pairs born between May 1985 and December 1986.³² The sample used included 1,232 individuals (519 boys; 713 girls), assessed for antisocial behavior at ages 16-17 and/or 19-20. No data was available on brain damage or chromosomal aberrations. The sample included 265 MZ twin pairs, 233 DZ twin pairs and 236 individuals without their co-twin. Zygosity determination is outlined in the original paper describing the population.³² The percentage of non-Caucasians (determined as above) was 0.81% (n=10). All participants provided written consent, and the Ethics Committee at Karolinska Institutet approved the study.

Measures of antisocial behavior

In the discovery sample, two self-rating instruments targeting antisocial behavior were available (see Supplementary material). Firstly, two subscales of the Life History of Aggression (LHA) were used. The LHA has excellent test-retest stability, inter-rater reliability, and internal consistency reliability.³³ It has been widely used to study violent behavior.^{34,35} The Aggression subscale consists of temper tantrums, physical fights, verbal aggression, physical assaults on people (or animals), and assaults on property (5 items). The Antisocial/Consequences behavior subscale quantifies school disciplinary problems, problems with supervisors at work, antisocial behavior involving or not involving the police (4 items). Each item is scored based on the frequency of the respective behaviors since adolescence, from 0 (no event) to 5 (so many events that they cannot be counted). The Aggression subscale score ranges from 0 to 25 points, and the Antisocial/Consequences subscale score from 0 to 20 points, with possible total combined scores from 0 to 45 points. Cronbach's alphas for the 5 Aggression items and the 4 Antisocial items were .78 and .57, respectively, and .76 for the total LHA scale.

Secondly, a questionnaire with 25 items derived from the Self-Reported Delinquency Questionnaire (SRD) and modified for CATSS was used.^{36,37} The SRD measures the frequency of three kinds of law-breaking behavior over the past 12 months: property offenses (e.g. shoplifting, breaking and entering, vandalism, etc.), violent offenses (assault, robbery, sexual violence, etc.), and drug-related offenses (use and distribution). Each item can be scored from 0 (never) to 4 (more than 10 times). We then subdivided these items into two subscales, labeled Overt Aggression (targeting another individual directly; 9 items), and Covert Aggression (not targeting another individual directly; 16 items). The total score ranged from 0 to 100, with the possible scores for the subscales being 0-36 (Overt Aggression) and 0-64 (Covert Aggression). Cronbach's alpha for the Overt Aggression and Covert Aggression subscales were .89 and .82, respectively, and .85 for the total SRD scale.

In the replication sample, only one measure of antisocial behavior was available, also derived from the SRD.³⁶ This version of SRD contains 30 items, and while measuring the same kinds of behavior,

the proportions of questions are slightly different from the version used in the discovery sample, and items regarding sexual violence are not present. The items were scored 0-5, with the same levels as in the discovery sample, but with an additional category “5” representing more than 50 times in the last 12 months. Cronbach’s alpha for the SRD in the replication sample was .92. The items were not subdivided, since too few questions in this sample represented overt aggression. Since there were two separate ages of data collection, with the 16-17-year-old twins having the most comprehensive coverage, scores from this age were used when available (n=1055), and scores from 19-20-year-olds were used when there were no scores available from the preceding age (n=177).

Genotyping

Eight SNPs, located in as well as up- and downstream of *OXTR*, were selected based on previous associations with antisocial behavior or other aspects of social behavior (see Table 1). In the discovery sample, DNA from saliva samples was extracted using OraGene® DNA self-collection kit (DNA Genotek, Inc., Ottawa, ON, Canada). Genotyping was then performed by LGC Genomics (<http://www.lgcgenomics.com>) using the KASPar® chemistry. In the replication sample, the genotyping of rs4564970 was performed as described above, while rs7632287 was genotyped with commercially available 5’ nuclease (TaqMan) assays on an ABI Prism 7900 HT instrument (Applied Biosystems, Foster City, California). The SNPs were not found to be in linkage disequilibrium with one another ($r^2 < .31$) and all SNPs were in Hardy-Weinberg equilibrium, as assessed using Haploview 4.2.³⁸ The genotyping success rate was >97% in both samples.

Statistical analyses

Associations between SNPs and the behavioral measures were estimated using a linear mixed effect model in the MIXED procedure of SAS 9.3 (SAS Institute, Inc., Cary, NC, USA), which enabled us to

adjust for the dependent nature of twin observations as well as the dependence of individuals from the same family (i.e. scores from all genotyped subjects were included in the analyses). Given that MZ twins, on average, share 100% of their genome while DZ twins share about 50%, we modeled two separate variance-covariance matrices: (1) for MZ twins, and (2) for DZ twins. By using R-side random effects with an unstructured variance-covariance matrix, correlations between individuals in groups (1) and (2) were calculated. The sample sizes allowed us to analyze boys and girls separately. Given the very low frequency of rs4564970 CC (n=13) and rs2254298 AA genotypes (n=25), these were grouped with their respective heterozygotes in the primary analyses. To control for multiple testing in the discovery sample, Bonferroni correction was used: analyses of eight SNPs, a total of four subscales, and two sexes separately, yielding 64 independent tests. As the significance level was set to .05, this resulted in a corrected p-value limit of .00078. We carried out combined analysis of the two samples by using MetaP³⁹, taking into consideration the direction of effects and sample sizes.

Results

Discovery sample

In the discovery sample, four SNPs (rs4564970, rs53576, rs2254298, and rs7632287) showed associations with the SRD scale at the .05 significance level (see Table 2). The associations between rs7632287 and SRD total score ($p=.00052$) and Overt Aggression score ($p=6.2 \times 10^{-7}$) in boys survived correction for multiple testing. We performed post-hoc tests between rs7632287 and SRD in a recessive model, resulting in a stronger association, where the AA genotype conferred significantly higher scores than the GA/GG genotypes on Overt Aggression ($p=1.5 \times 10^{-7}$), with a Cohen's effect size value of $d=.37$. No associations were found for rs75775, rs2268498, rs237887, or rs1042778.

Three SNPs (rs4564970, rs2254298, and rs7632287) showed associations with the LHA scale at the .05 significance level (see Table 3). The associations between rs4564970 and the Antisocial/Consequences subscale in all subjects ($p=.00013$, $d=.20$) and in boys only ($p=.00063$, $d=.28$) survived correction for multiple testing. The association between rs7632287 and total LHA score did not survive correction, but became stronger when tested in a recessive model ($p=.00069$, $d=.32$). No associations were found for rs75775, rs2268498, rs53576, rs237887, or rs1042778.

Replication sample

We tested the two SNPs which showed associations and survived multiple testing correction in the discovery sample, i.e. rs7632287 and rs4564970 – while the association between the latter and SRD did not survive correction, the association with LHA did, and since the correlation between the SRD and the LHA in the discovery sample was pronounced ($r=.594$; $p<.0001$) we chose to include rs4564970 in the replication attempt. Only boys were included in these analyses. The association between rs7632287 and total SRD score remained significant in a recessive model ($p=0.019$, $d=.39$). No associations were found between rs4564970 and SRD scores in the replication sample.

Combining the p-values of the two samples with regard to the association between rs7632287 and the SRD in boys further strengthened the association (Stouffer's z trend; $p=2.5 \times 10^{-5}$).

Analyses excluding non-Caucasians

The associations between SNPs and measures of antisocial behavior in both the discovery and replication samples remained significant in analyses without non-Caucasians.

Discussion

There is great interest in the neurobiological roots of antisocial behavior, but investigations into the genetic etiology have yielded few consistent results⁴⁰ (exceptions may include monoamine oxidase A⁴¹). The hypothesis of *OXTR* as a genetic risk factor for antisocial behavior has been explored, but so far by using small samples, or with results confined to interactions with e.g. past experiences or alcohol, alternatively linked to extreme subgroups. To our knowledge, the current study is the most comprehensive investigation to date exploring the link between *OXTR* and antisocial behavior as a continuous trait in the general population. It allowed us to identify an association between rs7632287, located downstream of *OXTR*, and antisocial behavior measured by the SRD scale, in two independent samples of adolescents. Carriers of two copies of the minor allele (A) displayed higher SRD score, particularly in the Overt Aggression domain compared to G allele carriers. In addition, the rare C allele of the independent SNP rs4564970, located in the 5' regulatory region of *OXTR*, was associated with higher scores on the Antisocial/Consequences subscale of the LHA scale – our other measure of antisocial behavior. These associations were all specific for boys and they survived correction for multiple testing.

The rs7632287 SNP has not previously been directly associated with antisocial behavior, but in a recent meta-analysis of 11 genetic association studies on *OXTR* and autism spectrum disorder (ASD)⁴² the A allele of rs7632287 showed a strong association with ASD impairments (including social impairments) in children. Walum and co-workers also demonstrated that the rs7632287 A-allele was associated with lower relationship quality, partner bonding, and lower social skills, across three normative samples.⁴³ The rs7632287 SNP is located downstream of *OXTR*, and may by itself influence transcription regulation, or be in linkage disequilibrium with a polymorphism of importance for the function or expression of the receptor. Intriguing in this context is that Malik and co-workers²³ found an association between childhood-onset aggression and rs6770632, which is located in the 3'-untranslated region of *OXTR*, and according to 1000 Genomes data⁴⁴ is in strong linkage disequilibrium with rs7632287 ($D'=1$, $r^2=0.951$).

Although rs4564970 was strongly associated with antisocial behavior as measured by the Antisocial subscale of the LHA, it was not associated with SRD in the replication sample. The SRD and the LHA are strongly correlated, but not perfectly so, and may be regarded as measuring slightly different phenotypes. The LHA deals more with direct aggression and rage than does the SRD, and the Antisocial/Consequences subscale focuses on the consequences of one's actions, such as being fired or arrested. Hence, a more direct replication utilizing LHA may be necessary to validate this finding. Even though rs4564970 has not been heavily scrutinized, it has been shown to interact with alcohol consumption in relation to anger and aggressive behavior,^{19,20} and has also been nominally associated with ASD.⁴⁵ It is located in close vicinity to the transcription start of *OXTR*, where several transcription factor binding sites are found.⁴⁶ Interestingly, Loth and co-workers recently showed an interaction between rs237915 and stressful life events on ventral striatal activity and peer problems in boys,²⁸ and this SNP is located within 100 nucleotides from rs4564970 ($D'=1$, $r^2=.04$).

In line with previous genetic studies⁴⁷ we found sex-specific associations, which reiterates the established sexual dimorphism of the oxytocin system, underscored by the well-established sex differences in the oxytocin system.⁴⁸⁻⁵⁰ Since OXT, as described in the Introduction, acts as a prosocial mediator in both humans and rodents it does not seem farfetched to believe that a dysfunction of OXT signaling may contribute to antisocial behaviors. Indeed, an inability to synthesize OXT¹⁴ or *OXTR*⁵¹ generates aggressive behavior in mice, and Calcagnoli and co-workers have repeatedly demonstrated that exogenously administered oxytocin exerts anti-aggressive effects in male rats.⁵²⁻⁵⁵ Intriguing studies measuring e.g. CSF oxytocin levels¹⁸ or epigenetic regulation of the *OXTR* locus^{25,26} confirms this notion in humans. The knowledge of the neural circuitry mediating oxytocin's anti-aggressive effect is sparse, but an involvement of hypothalamus and amygdala,⁵⁶ as well as the neurotransmitter serotonin, has recently been suggested.⁵⁷

Some limitations of our study should be considered. Using two different versions of the SRD prevented us from attempting a replication of the Overt Aggression subscale, and a larger replication

sample, using exactly matched instruments would perhaps have allowed us to find a much stronger association. Ethnicity is difficult to ascertain with any real certainty, based solely on the birth countries of parents. More detailed information on ethnicity would have been desirable, to avoid stratification. The response rate in CATSS at 18 years of age was 50%, and reasonably the most violent-prone individuals are overrepresented in the non-responders. However, given the notion that aggression exists on a continuum, this has reasonably attenuated our results but is not necessarily a threat to the validity of the findings. Furthermore, the assessments of behavior were performed using self-rating instruments, which may lead to potential bias due to the participants' own memory of events or honesty. Future studies using larger sample sizes are not only warranted in order to replicate our positive findings, but also to provide power to unravel if the nominal associations between rs4564970, rs53576, rs2254298, rs7632287, and measures of antisocial behaviors seen in the discovery sample are true or not. Furthermore, more comprehensive genotyping efforts are warranted to identify functional variants, and to capture the full genetic contribution of the *OXTR* to antisocial behavior. In line with recent studies,^{25,26} inclusion of measures of epigenetic and environmental factors would also have provided a more complete picture of how *OXTR* may contribute to antisociality.

Conclusions

We have demonstrated an association between the *OXTR* SNP rs7632287 and antisocial behavior in adolescent boys in two samples drawn from the general population. A tentative and independent association between rs4564970 and antisocial behavior was also found. Further replication of our results could provide a specific genetic risk factor for committing violent acts, as well as be crucial to understanding how aberrant social behavior arises, and lend support to the potential role of *OXTR* as one target in treatment of aggressive antisocial behavior.

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Author Contributions: Dr Hovey had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Hovey, Westberg, Lichtenstein, Anckarsäter, Lundström. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Hovey. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Hovey, Lindstedt, Johansson. Obtained funding: Westberg, Anckarsäter, Lundström, Lichtenstein. Study supervision: Westberg.

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Table 1. SNP Information

SNP	MAF	Position	Examples of previous associations
rs75775	0.15 (T)	5'	Autism ⁵⁸
rs2268498	0.45 (C)	5'	Empathy, ^{59,60} emotion recognition ⁶¹
rs4564970	0.06 (C)	Intron 1	Aggressive behavior ^{19,20}
rs53576	0.34 (A)	Intron 3	Empathy, ⁶² prosociality, ⁶³ parenting, ⁶⁴ amygdala activation ⁶³
rs2254298	0.10 (A)	Intron 3	Prosociality, ⁶⁵ autism, ⁴² amygdala size, ⁶⁶ empathy ⁶⁷
rs237887	0.41 (G)	Intron 3	Social recognition, ⁶⁸ empathy, ⁶⁷ autism ⁴²
rs1042778	0.38 (T)	3'UTR	Prosociality, ⁶⁵ autism, ⁴⁶ aggression ²³
rs7632287	0.26 (A)	3'	Pair-bonding, ⁴³ autism ⁴²

SNP: single nucleotide polymorphism; MAF: minor allele frequency; UTR: untranslated region.

Table 2. Positive associations between *OXTR* variants and Self-Reported Delinquency (SRD) in the discovery sample (CATSS).

SNP	Genotype (n: boys/girls)	SRD			Overt Aggression			Covert Aggression		
		All	Boys	Girls	All	Boys	Girls	All	Boys	Girls
<i>OXTR</i> rs4564970	CC/CG (124/147)	7.08 (7.48)	8.62 (8.77)	5.79 (5.92)	1.31 (2.35)	1.82 (2.93)	0.88 (1.59)	5.77 (5.88)	6.80 (6.70)	4.91 (4.95)
	GG (870/1171)	5.89 (6.67)	6.86 (7.36)	5.17 (6.01)	0.92 (2.06)	1.29 (2.32)	0.65 (1.79)	4.96 (5.25)	5.57 (5.75)	4.51 (4.79)
	p	0.015	0.019	n.s.	0.015	n.s.	0.039	0.023	0.024	n.s.
<i>OXTR</i> rs53576	AA (125/160)	5.09 (4.81)	5.57 (4.95)	4.71 (4.67)	0.68 (1.25)	0.94 (1.50)	0.48 (0.97)	4.40 (4.18)	4.62 (4.10)	4.23 (4.24)
	GA (432/589)	6.21 (7.10)	7.62 (8.52)	5.18 (5.64)	1.05 (2.21)	1.53 (2.71)	0.69 (1.67)	5.16 (5.55)	6.08 (6.56)	4.49 (4.56)
	GG (438/560)	6.17 (6.92)	7.06 (7.12)	5.48 (6.69)	0.97 (2.17)	1.29 (2.29)	0.72 (2.04)	5.21 (5.42)	5.77 (5.61)	4.76 (5.23)
	p	0.048	0.0092	n.s.	n.s.	0.012	n.s.	n.s.	0.028	n.s.
<i>OXTR</i> rs2254298	AA/GA (199/218)	6.48 (6.84)	7.43 (7.65)	5.62 (5.88)	1.17 (2.20)	1.55 (2.59)	0.83 (1.69)	5.31 (5.33)	5.88 (5.80)	4.79 (4.82)
	GG (790/1092)	5.93 (6.77)	7.02 (7.54)	5.15 (6.03)	0.92 (2.07)	1.30 (2.35)	0.65 (1.79)	5.01 (5.35)	5.72 (5.93)	4.50 (4.82)
	p	n.s.	n.s.	n.s.	n.s.	n.s.	0.023	n.s.	n.s.	n.s.
<i>OXTR</i> rs7632287	AA (88/69)	7.32 (9.57)	9.68 (11.79)	4.30 (3.95)	1.48 (3.19)	2.44 (3.98)	0.25 (0.58)	5.84 (6.99)	7.24 (8.49)	4.06 (3.75)
	GA (386/502)	5.81 (6.46)	6.37 (6.01)	5.39 (6.77)	0.90 (2.06)	1.09 (1.81)	0.75 (2.23)	4.92 (5.05)	5.28 (4.95)	4.64 (5.11)
	GG (525/746)	6.02 (6.51)	7.21 (7.60)	5.19 (5.47)	0.94 (1.92)	1.36 (2.39)	0.65 (1.44)	5.08 (5.26)	5.85 (5.98)	4.54 (4.62)
	p	0.021	0.00052*	n.s.	0.00097	6.2 ⁻⁷ *	n.s.	n.s.	0.012	n.s.
	p^{recessive}	0.0065	0.00031	n.s.	0.00021	1.5 ⁻⁷	n.s.	0.026	0.0076	n.s.

Means (SD). P-values are uncorrected. p^{recessive}: rs7632287 AA carriers tested against GA/GG carriers. Results significant after correction for multiple testing marked with an asterisk.

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Table 3. Positive associations between *OXTR* variants and Life History of Aggression (LHA) in the discovery sample CATSS

SNP	Genotype (n: boys/girls)	LHA			Aggression			Antisocial/Consequences		
		All	Boys	Girls	All	Boys	Girls	All	Boys	Girls
<i>OXTR</i> rs4564970	CC/CG (121/148)	7.90 (6.30)	8.82 (7.30)	7.14 (5.25)	7.11 (5.22)	7.78 (5.84)	6.56 (4.59)	0.79 (1.78)	1.04 (2.21)	0.58 (1.30)
	GG (871/1166)	6.80 (5.71)	7.41 (6.10)	6.35 (5.35)	6.33 (5.08)	6.88 (5.43)	5.92 (4.75)	0.47 (1.29)	0.53 (1.36)	0.42 (1.24)
	p	0.0045	0.029	n.s.	0.029	n.s.	n.s.	0.00013*	0.00063*	n.s.
<i>OXTR</i> rs2254298	AA/GA (198/218)	7.56 (6.23)	7.71 (6.86)	7.41 (5.60)	6.92 (5.34)	7.02 (5.81)	6.84 (4.88)	0.63 (1.61)	0.70 (1.86)	0.57 (1.34)
	GG (789/1088)	6.75 (5.66)	7.51 (6.09)	6.20 (5.27)	6.28 (5.03)	6.95 (5.39)	5.80 (4.71)	0.47 (1.29)	0.56 (1.39)	0.41 (1.21)
	p	0.026	n.s.	0.0073	0.046	n.s.	0.0084	0.032	n.s.	n.s.
<i>OXTR</i> rs7632287	AA (86/68)	7.90 (6.45)	9.48 (7.36)	5.91 (4.37)	7.23 (5.43)	8.50 (6.00)	5.62 (4.12)	0.68 (1.70)	0.98 (2.13)	0.29 (0.75)
	GA (386/500)	6.58 (5.36)	7.04 (5.51)	6.22 (5.22)	6.16 (4.89)	6.64 (5.13)	5.79 (4.66)	0.42 (1.09)	0.40 (1.04)	0.43 (1.13)
	GG (525/745)	7.01 (5.93)	7.63 (6.53)	6.58 (5.43)	6.47 (5.17)	6.96 (5.61)	6.12 (4.81)	0.54 (1.46)	0.67 (1.64)	0.45 (1.33)
	p	0.022	0.0025	n.s.	0.047	0.010	n.s.	0.041	0.0020	n.s.
	p^{recessive}	0.022	0.00069	n.s.	0.039	0.0025	n.s.	n.s.	0.0048	n.s.

Means (SD). P-values are uncorrected. p^{recessive}: rs7632287 AA carriers tested against GA/GG carriers. Results significant after correction for multiple testing marked with an asterisk.

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Table 4. Positive associations between *OXTR* variants and Self-Reported Delinquency (SRD) in the replication sample (TCHAD; boys only)

SNP	Genotype (n)	SRD
		Boys
<i>OXTR</i> rs4564970	CC/CG (62)	3.45 (4.18)
	GG (443)	4.08 (7.03)
	p	n.s.
<i>OXTR</i> rs7632287	AA (31)	7.06 (9.89)
	GA (200)	3.49 (6.00)
	GG (278)	3.97 (6.71)
	p	0.055
	p^{recessive}	0.019

Means (SD). P-values are uncorrected. p^{recessive}: rs7632287 AA carriers tested against GA/GG carriers.

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